Chapter 1

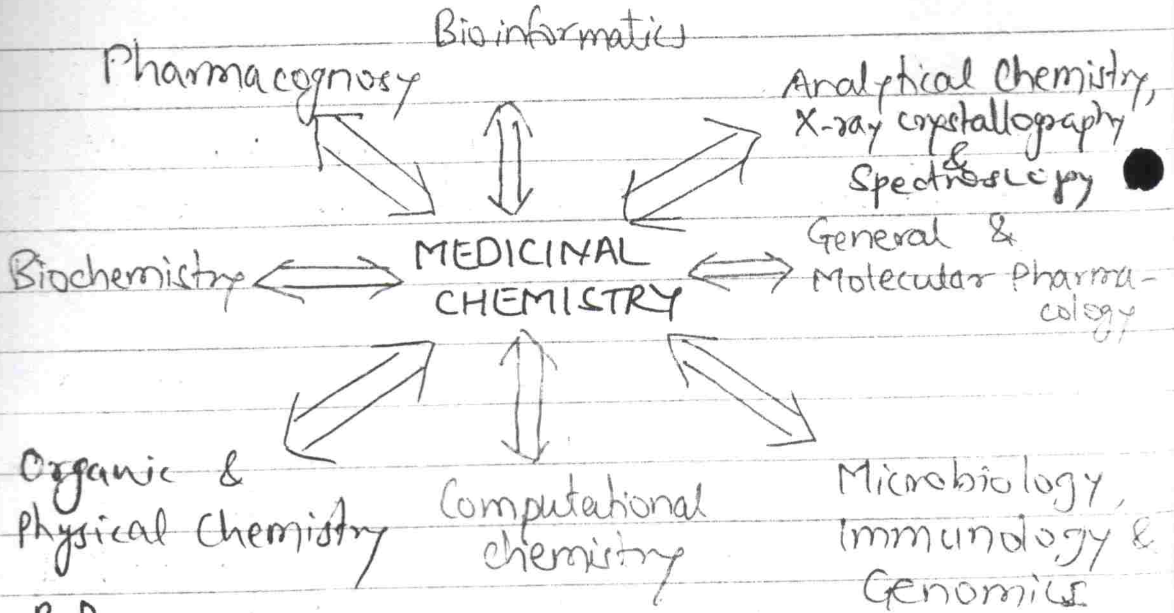
Introduction to Medicinal Chemistry

Medicinal chemistry as a subject explains the design and production of ~~com~~ organic compounds that can be used for the prevention, treatment or cure of diseases. According to Burger, "medicinal chemistry tries to be based on the ever-increasing hope that biochemical rationales for drug discovery may be found." In practice medicinal chemistry is based on the hope of discovering biochemical pathways as well as modification of structures ~~with~~ having known ~~physicochemical~~ physiologic or pharmacologic ~~eff~~ effects.

The primary function of medicinal chemist is still to discover new drugs and the knowledge ~~of~~ principles of biochemical action are proving to be very helpful for design of new drug molecules.
In the ancient period, natural products having history as folk medicine were used for drug therapy but now a days very little of these remedies are used. The molecular orbital and other calculations that elucidate the electronic and conformational aspects of molecules are now used to predict the

tional structures for selective biological activity.
The first use of synthetic organic chemicals ~~began~~ for therapy began in early nineteenth century with the use of chloroform & ether for anesthesia. The late nineteenth century was dominated by Paul Ehrlich. This period saw tremendous development in medicinal chemistry.
Now a days the drug discovery process is a team work which includes scientists from various disciplines, including biology, toxicology, pharmacology, microbiology & biopharmacy.

figure 1.1 Contributors to medicinal chemistry.



Reference
M.E. Wolff, Burger's Medicinal chemistry, 5th ed., Part I, The Basis of Medicinal chemistry, New York, Wiley-Interscience,

Chapter 2

Physico-chemical Properties and Drug Activity.

Physico-chemical properties refer to the influence of the organic functional groups present within a molecule on its acid / base properties, water solubility, crystal structure, partition coefficient, etc.
In design of better medicinal agents the relative contributions of each functional group adds to the overall physical and chemical properties of the molecule.

Selectivity of Drug Action at Active Site

Ehrlich gave the concept of drug receptor. It stated that certain "side chains" on the surface of cell were "complementary" to the drugs and hence allow the two substances to combine.
The selectivity of drug action was shown via the concept of "magic bullet" for compounds that diminish the disease states without producing unwanted harm to the organism being treated.
The structural elements (functional groups) within a molecule contribute in an additive manner to the physico-chemical properties of a molecule and hence to its biological action.

Physico-chemical Properties of Drug Molecules.

The most pharmacologically influencial physico-chemical properties include :

(a) Acid - Base properties
(b) Relative Acid Strength [pka]
(c) Water Solubility
(d)

Acid - Base Properties

when considering the solution behaviour of drug within the body, we deal with dilute solutions. Lowry - Bronsted acid-base theory explains and predicts the acid / base behaviour of drug molecules.

The acid-base properties of drug molecules directly affects absorption, excretion and compatibility of drug with other drugs in solution. According to Bronsted theory, acid is any substance capable of donating proton $[H^+]$ in solution whereas base is any substance capable of accepting proton (H^+) in solution. The acid gives a proton to base and is thus converted into its conjugate base.

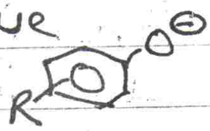
Example: $\underset{\text{(Acid)}}{CH_3COOH} + \underset{\text{(Base)}}{H_2O} \rightleftharpoons \underset{\text{Conjugate Base}}{CH_3COO^{\ominus}} + \underset{\text{Conjugate Acid}}{H_3O^{\oplus}}$

The base on the other hand, accepts a proton from and acid & is converted into its conjugate acid.

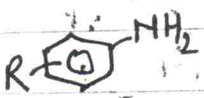
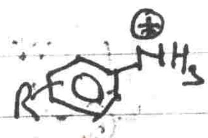
Example: $CH_3NH_2 + H_2O \rightleftharpoons CH_3NH_3^{\oplus} + OH^{\ominus}$

[Base] [Acid] Conjugate Acid, Conjugate Base

When an acid loses its proton, it has extra pair of electrons which donot neutralize by the proton. This is the ionized form of an acid and is highly water soluble ~~b~~ due to charge. The acid is said to ~~be~~ have undergone dissociation.

	Acid		Conjugate Base	
1.	Phenol		Phenolate	
2.	Alkyl thiol	R–SH	Thiolate	$R-S^{\ominus}$

When a base is converted to its conjugate acid, it is also ionized and carries a positive charge due to extra proton. Most basic drugs are usually derivatives of primary, secondary and tertiary amines.

	Base		Conjugate Acid	
1.	Aryl Amine		Aryl Ammonium	
2.	Imine	$R-C(H)=N-H$	Iminium	$R-C(H)=NH_2^{\oplus}$

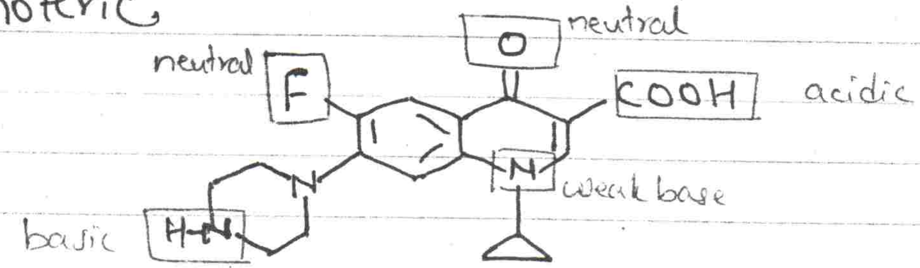
Organic functional groups that neither give up a proton nor accept a proton are said to be neutral with respect to acid-base properti-

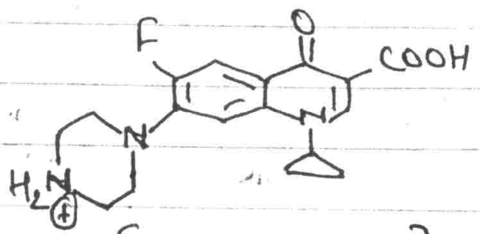
Examples:

$R-CH_2OH$	$R-O-R$	$R-C\equiv N$
Alkyl Alcohol	Ether	nitrile

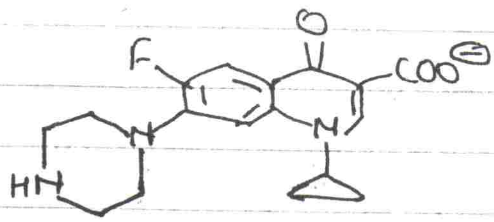
A molecule may contain multiple functional groups and therefore possess both acidic and basic properties.

For example ; Ciprofloxacin. It contains secondary amine and a carboxylic acid group. Depending on pH of the solution, the molecule can either accept or donate a proton or both. Thus it can be acidic, basic or amphoteric.





[At pH 1.0-3.5]



At a given pH value only one functional group is ionize

Relative Acid Strength [pk_a]

The concept of pk_a indicates the relative acid / base strength of organic functional groups and allows to calculate, for a given pH, the amount of molecule in the ionized and unionized form.

Strong acids and bases dissociate or accept proton to produce their respective conjugate bases and acids.

$$NaOH + H_2O \rightleftharpoons Na^{\oplus} + OH^{\ominus} + H_2O$$

$$HCl + H_2O \rightleftharpoons Cl^{\ominus} + H_3O^{\oplus}$$

Water is amphoteric. In dilute aqueous solution, the strongest base present is $OH^{\ominus}$ and the strongest acid is $H_3O^{\oplus}$. This is called as levelling effect of water.

Predicting the degree of ionization of a molecule

To predict the degree of ionization of any molecule, the pk_a values of the acidic and basic functional groups present in the molecule should be known.

Handerson - Hasselbach equation is used to calculate the percent ionization of compound at a given pH.

$$pk_a = pH + \log \frac{[\text{acid form}]}{[\text{base form}]}$$

ed.

The percent ionization of a drug is calculated using Eq. 1-1 for HA acids (nonionized) and Eq. 1-2 for BH^+ acids (ionized).

$$\% \text{ ionization} = \frac{100}{1 + 100^{(pka - pH)}} \qquad (Eq. 1\text{-}1)$$

$$\% \text{ ionization} = \frac{100}{1 + 100^{(pH - pk_a)}} \qquad (Eq. 1\text{-}2)$$

Table 1-1 gives an index of the effect of pH & pk_a on the percentage ionization of ~~HA~~ HA acids and BH^+ acids.

Table 1-1

Percentage Ionization Relative to pka

	Ionization (%)	
	HA Acids	BH^+ Acids
$pk_a - 2$ pH units	0.99	99.0
$pk_a - 1$ pH unit	9.1	90.9
$pk_a = pH$	50.0	50.0
$pk_a + 1$ pH unit	90.9	9.1
$pk_a + 2$ pH units	99.0	0.99

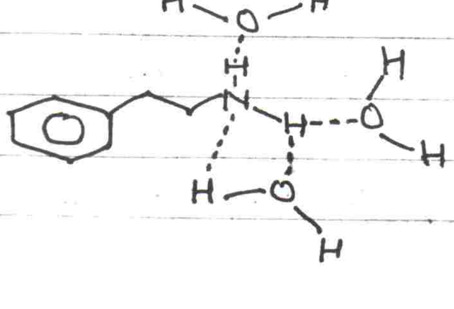
pk_a affects the distribution of drug molecule in various tissues of the body.

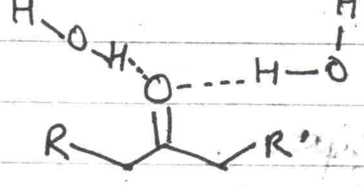
Water Solubility of Drugs

The solubility of drug molecule in ~~dr~~ water affects the routes of administration, absorption, distribution and elimination.
The hydrogen bonding potential in the molecule and the ionization of functional groups are considered in study of water solubility of molecules.

Hydrogen Bonding

Each functional group capable of donating or accepting a hydrogen bond contributes to overall water solubility of the compound. Such functional groups increase the hydrophilic nature of molecule.
When two molecules containing dipoles approach one another, they align such that the negative end of one dipole is electrostatically attracted to the positive end of the other. If the positive end of dipole is Hydrogen atom, it is called as hydrogen bonding.
For a Hydrogen bond to ~~occ~~ occur at least one dipole must contain an electropositive hydrogen atom.
Several possible H-bond types may occur with different organic functional groups and water.





More the hydrogen bonds, the higher is the water solubility.
Table 1-2 exemplifies certain function groups and their potential ~~no.~~ ~~of~~ number of H-bonds.

Table 1-2
Functional Groups and H-bonding

Function Group	Number of Potential H-bonds
R–OH	3
R–NH_2	3
R–C(=O)–R'	2
R–N(R')–H	2
R–N(R'')–R'	1

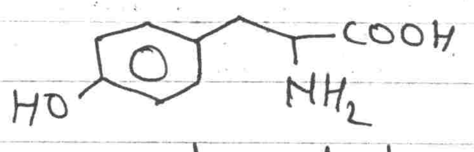
Ionization

Ion-dipole bonding plays an important role in determining the water solubility of molecule.
Ion-dipole bonds develop between a cation or anion and a formal dipole like water.
A cation associates with negative end of the dipole.
An anion associates with positive end of the dipole.
In ion-dipole bonds, as in organic salts, to

associate with enough water molecules to become water soluble, the salt must be highly dissociable.
Highly dissociable salts are formed from
(a) strong acid and strong base
(b) weak acid and strong base
(c) strong acid and weak base

The strongest acids are HCl, HNO_3, H_2SO_4, perchloric and performic acid.
The strongest bases are $NaOH$ and KOH.

Compounds with ionizable functional groups that produce opposite charges can interact with each other rather than water. Such compounds are water insoluble.
For Example; Amino acid Tyrosine



Greater the separation between charges, higher the water solubility of molecule.

Predicting Water Solubility

1. Empiric Approach :- It is based on the carbon solubilizing potential of the functional groups.

More the hydrogen bonds, the higher is the water solubility.
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In ion-dipole bonds, as in organic salts, to

If the solubilizing potential is more than the total number of carbon atoms in the molecule, the molecule will be water soluble.
Functional groups that can form intramolecular H-bonds decrease the solubilizing potential and therefore decrease the water solubility.

2. Analytical Approach :- It involves the calculation of approximate Log P value or the log of the partition coefficient of the molecule.

Partition Coefficient

It is the ratio of the concentration of drug in octanol to that in water.
Log P is a measure of the solubility characteristics of molecule.
A hydrophobic / hydrophilic value [hydrophobic substituent constant, π] is given to each functional group.

$$\text{Log } P = \Sigma \pi$$

Water solubility is the solubility of more than 3.3% ; equivalent to about 0.5 Log P.

Log P values less than +0.5 tend to increase water solubility and Log P values more than +0.5 tend to decrease water solubility.

Ionization state of a molecule influences its water solubility and the ability of the molecule to traverse biological membranes and hence its ability to get absorbed in body.

Chapter 3

Stereochemical Features and Pharmacological Activity

The physicochemical properties of a drug molecule are dependent upon the functional groups present in the molecule and their spatial arrangement (stereochemistry).
A drug molecule is subjected to many complex processes from its administration to elicitation of biological response (fig. 3-1)

Figure 3-1 Drug Administration to Biological Response

Stereochemistry of the molecules play a major role in the pharmacological properties, as many of these processes are stereospecific. Stereochemistry is responsible for the difference in degree of pharmacological activity of isomers. ~~The structural features required~~

The influence of steric factors on pharma-

~~cot~~ cological action is categorised in three groups —
(1) Optical and geometric isomerism
(2) Conformational isomerism
(3) Isosterism & pharmacological action.

~~Optical Isomerism~~

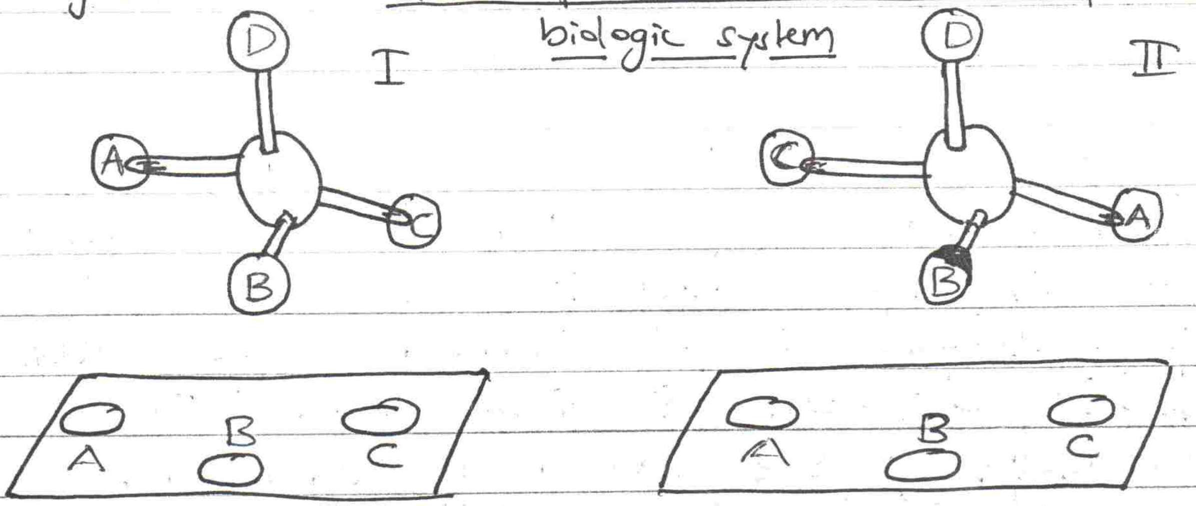
Optical & Geometric Isomerism And Pharmacological Activity.

Optical Isomerism
Optical isomers are compounds that differ only in their ability to rotate the plane of polarized light. Optical isomers may exhibit different biological activities. For example, one isomer of ammonium tartarate inhibits the growth of Penicillium glaucum whereas the other isomer has no effect.
Optical isomers may be enantiomers or diaster-eomers.
Enantiomorphs are non-superimposable mirror images. They rotate the plane of polarized light in equal amounts but in opposite directions
Diastereomers are isomers that are neither mirror images nor super-imposable.

Influence of optical Isomerism on Pharmacological Activity.

The differences in biologic activity between optical isomers depends on their ability to react selectively at an ~~asym~~ asymmetric center in the biological system. ~~The~~ Figure 3-2 exemplifies the affect of these difference.

Fig. 3-2 Effect of Isomeric structure ~~&~~ on biologic system



Of the two isomers shown in above figure, only one (I) has the correct orientation for all the three groups to fit at their respective sites on the biological system (receptor) and therefore only (I) is active biologically. This is called as Easson - Stedman Hypothesis or the three point fit hypothesis.

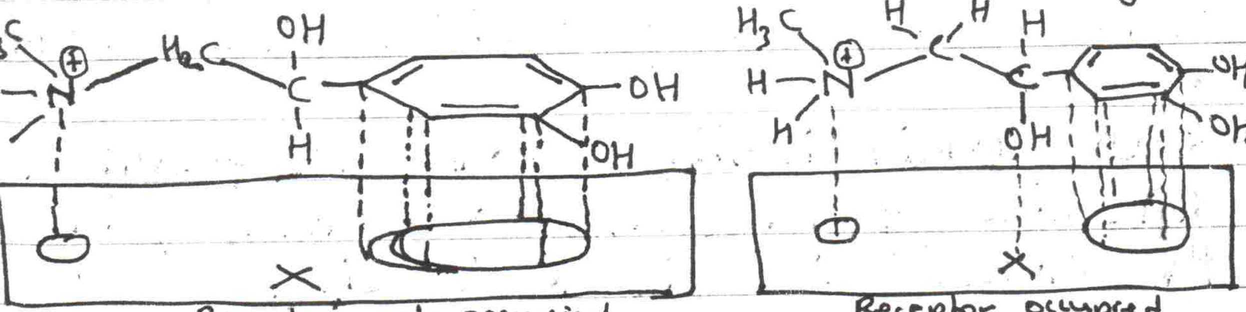
The differences in distribution of the isomers in the biologic system may also lead to the

differences in pharmacological activities. The differences in distribution occurs because the isomers may be selected by some other asymmetric center in the system before it reaches the specific receptor. Figure 3-3 shows the selective phases that an isomer is subjected to before reaching the specific receptor.

Fig. 3-3 Selective processes in Drug Action.

Drug Dose ⇒ Membrane Selectivity ⟹ Selective Metabolism ⇓ Non specific receptor. [Site of Loss] ⟸ Drug Receptor ⟸ Desired Response

For example, only the (−) isomer of epinephrine has the −OH group in correct orientation to allow perfect binding with all groups to the receptor. Hence (−) epinephrine has high pressor activity whereas the (+) epinephrine is lost in distribution & has minimal activity.



Receptor not occupied
(+) Epinephrine less activity

Receptor occupied
(−) Epinephrine − More Active

Stereochemistry plays role in the metabolism of optically active drug molecules. On binding with racemic drugs, the metabolizing enzymes produce diastereomeric complexes and therefore lead to different rates of metabolism: stereo-selective meatabolism. A metabolized drug may have increased or decreased activity. For example, L-(+) lactoylcholine hydrolyzes much readily than D-(-) lactoyl choline.

Selectivity of passage of drug through membrane occurs due to asymmetric centers within the membrane. If the drug has to cross the membrane to reach its receptor, then selectivity at the membrane is important in biological activity. The transfer of molecules across a membrane by Permeases is a selective process.
For example, only L-isomer of valine, leucine penetrate the cell wall of bacteria such as E.coli wherear the D-isomers do not.

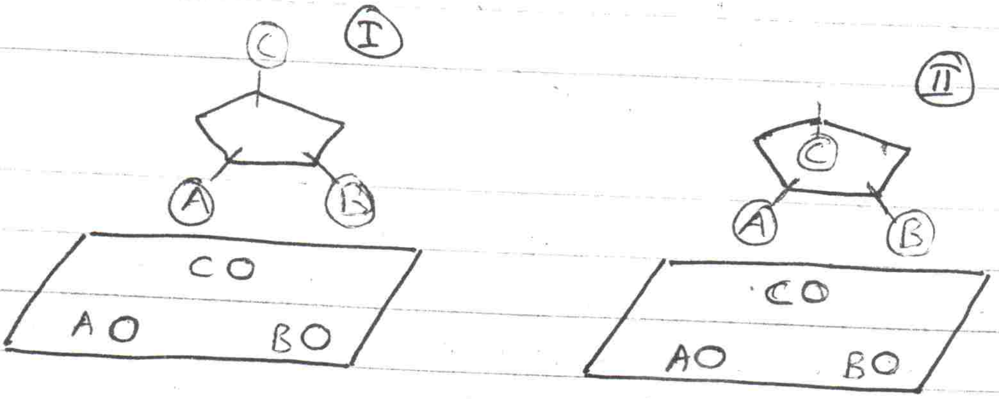
Geometric Isomerism [cis-trans isomerism]
It indicates a type of diastereomer that occurs as a result of restricted rotation around a bond.
When certain identified groups are present on same side of the plane of molecule, the the molecule is said to be cis.

when the identified groups are on opposite sides of the plane, then the molecule is said to be trans.

Influence of Geometric Isomerism on Biologic Activity

The effect of geometric Isomerism at the receptor site is shown in figure 3-4

Fig. 3-4 : Geometric isomers on receptor site



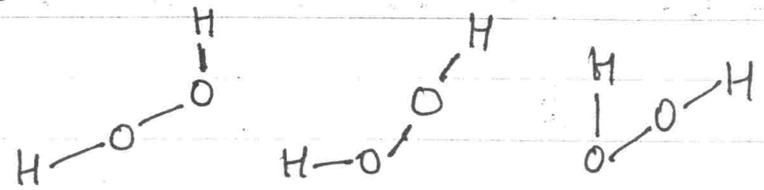
'C' is trans to A & B

All cis

Three substituents of cyclopentane ring (A, B & C) are needed for binding to the receptor surface. Only the 'cis' arrangement (II) allows this and hence it gives biologic activity.
For example, trans-Diethyl stilbesterol is 14 times active than the cis-isomer.
The differences in biologic activity of geometric isomers may be due to differences in interatomic distance of the groups essential for pharmacologic response.

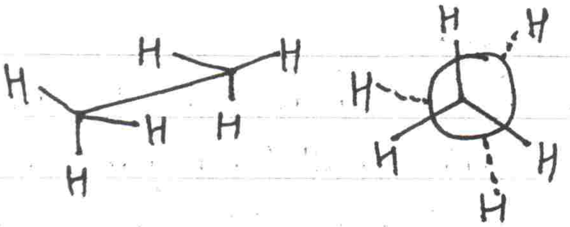
Conformational Isomerism And Biologic Activity

Conformational isomerism is defined as the non-identical spatial arrangement of atoms in a molecule, resulting from rotation about one or more single bonds. For example, Hydrogen Peroxide (H_2O_2) gives distinct conformations on rotation about the O—H bond.

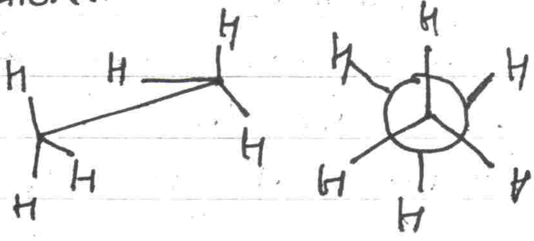


Drug molecules are complex structures. The barrier to free rotation about single bonds in drugs is due to the decreasing distance between the H-atoms on the adjacent carbon atoms as the C–C bond is rotated.

For example, E in eclipsed conformation, the hydrogen atoms are in closest proximity and hence the molecule is unstable. The staggered conformation, on the other hand, ~~gives~~ allows the greatest separation of hydrogen atoms and hence is the most stable conformation.

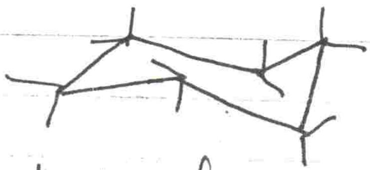


Eclipsed

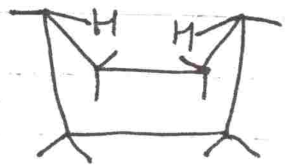


Staggered

Cyclo hexane exists in two conformations: hair and boat. The chair conformation s preferred over boat because in chair onformation all the bonds are staggered.



chair form



Boat form

n substituted rigid molecules, the axial substi- ents are in entirely different environment from uatorial substituents and therefore differences in ysical or chemical properties.

Influence of Conformational Isomerism on Biologic Activity

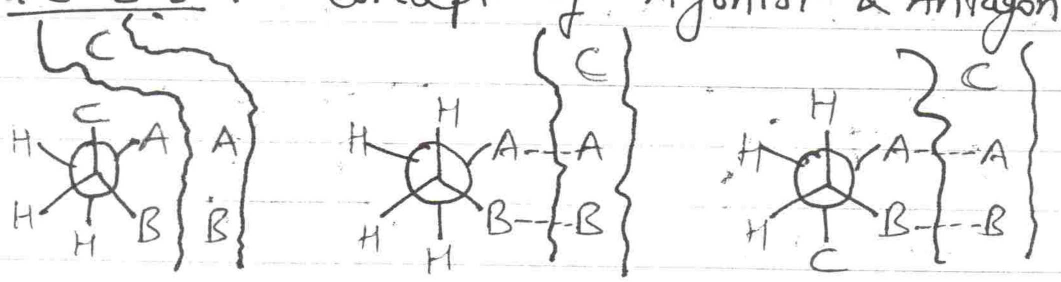
Jpon interaction with substrate, the enzymes ndergoes conformational change. Similarly on interaction with drug molecules, the receptor ndergoes conformational change.

receptor site may bind to only one of the any conformations of a drug molecule. The olecules that can adapt the conformation eded for binding for binding may act as onist or antagonists.

Antagonists bind to receptor but donot elicit ponse due to lack of some groups.

For example, groups A & B are needed for binding to receptor and C is needed for response (Figure 3-5)

Figure 3-5 : Concept of Agonist & Antagonist



I. Agonist

II. Antagonist
No 'C' group; which is needed for response

III. Antagonist & optical isomer of I. Can bind but no response

Conformational ~~isomers~~ analysis explains the differences in biologic activity of diastereomeric drugs.

Isosterisms and Pharmacological Action

Isosterism relates to the similarity in physicochemical properties of atoms, groups, radicals and molecules with similar electronic structures.

Grimm's concept of hydride displacement

Vertical columns of isosteric groups are formed by displacing one place to the right successively the elements of a row & adding a hydrogen atom.

Molecules of an isosteric pair should fit in the same crystal lattice.

Table 3-1 :

Isosteric Pairs of Grimm's Concept

C	N	O	F	Ne
	CH	NH	OH	HF
		CH_2	NH_2	OH_2
			CH_3	NH_3
				CH_4

Each vertical column represents a group of isosteres.

Bio isosterism

Application of the concept of isosterism to modify the biological activity is called as bioisosterism.

Classification of Bioisosteres

I. Classical Bioisosteres

(1) Monovalent atoms or groups. Example, halogens & $-XH_n$, X is C, N, O & S

(2) Divalent atoms or groups. Example, R–O–R' ; R–NH–R'

(3) Trivalent atoms or groups. Example, R–N=R' ; R–CH=R'

(4) Tetra substituted atoms. Example, =C= ; =N= ; =P=

(5) Ring Equivalents. Example, –CH=CH– ; –S– ; –O– ; –NH ; $-CH_2$

II. Non-classical Bioisosteres

(1) Cyclic vs noncyclic bioisosteres.
Example, promethazine ⟶ methdilazine

(2) Exchangeable Groups
- (a) Hydroxyl group bioisosteres
- (b) Carbonyl group bioisosteres
- (c) carboxylate group bioisosteres
- (d) Amide group bioisosteres
- (e) Thiourea bioisosteres
- (f) Halogen bioisosteres

Chapter 4

Drug Receptor Interactions

lost of the pharmacologically active agents
re structurally specific drug molecules.
ertain features of the chemical structure
pear to be having greater influence on
drug effect. A direct interaction of drug
th receptor material initiates a sequence
events leading to response.
receptor is defined as a tissue
mponent which fulfils the following
iteria —
it is a macromolecule which has
tes having chemorecognitive properties for a
ecific natural endogenous molecule or for
ecific drugs;
the specificity for sites on receptor and the
inction of the receptor are genetically determined
binding of agonists [endogenous substance /
ug] initiates a chain of events leading
response; and
the binding of agonist at the receptor
e doesnot depend on any bond making or
eaking in the agonist molecule.

e interaction of a drug with receptor may be
plained by the following equation

$$D + R \rightleftharpoons [DR] \longrightarrow \text{Response} \quad - \text{Eq. 4-1}$$

The quantitative ability of a drug to interact vith the receptor is called as <u>affinity</u>.
The ability of the drug, once bound to the receptor, to produce its biological response is alled as its ~~extrinsic~~ <u>intrinsic activity</u> or <u>efficacy</u>.

<u>Types of Drug - Receptor [DR] Interactions</u>.

The interaction of many structurally specific rugs with receptor is as under.

$$D + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} DR \xrightarrow[k_3]{} E \qquad \text{Eq. 4-2}$$

he two step sequence involves an equilibrium etween the drug and receptor. Both steps are trongly influenced by drug-receptor bonding & by stereochemical fit of the drug on he receptor. The forces involved in the bonding f drug and receptor include covalent bonds, nic, re-inforced ionic, hydrogen bonds, ion-dipole, ipole -dipole [keesom] forces, Van der Waals London forces (induced dipole-induced dipole)] and Deybe's forces (dipole-induced dipole)] and the ydrophobic interactions.

<u>Covalent Bonds</u>

Mutual sharing of electron pairs between wo atoms produces a covalent bond.

The bond strength of a covalent bond is 40 – 140 kcal / mol. Such bonds do not cleave spontaneously under physiological conditions. Cleavage occurs under enzymatic or specific acid-base catalysis. The effect of drug terminates once the drug-receptor bond has cleaved.
Chemical mechanism that lead to covalent bond formation between drug and receptor include alkylation, acylation & phosphorylation. For example, the reactive immonium-ion intermediate of anticancer nitrogen mustards [chlorambucil] readily forms covalent bonds with sulfhydryl, carboxylate and phosphate anions and with uncharged N, S & O atoms. Covalent bonds may produce irreversible effects.

Non-Covalent Bonds

These bonds produce short-lived & reversible interactions. They have low bond strengths.

(1) Ionic Bond.

~~These are~~ is formed by transfer of electrons. It is the electrostatic attraction between the oppositely charged ions. The bond strength is 5 kcal/mol. Functional groups such as α-carboxyl [terminal], secondary phosphoryl, α-ammonium terminal present on receptors; and aliphatic amino, quaternary ammonium

groups present in drugs are ionized at the physiological pH and ~~need~~ lead to the formation of ionic bonds.

(2) Hydrogen Bonds.

It is a strong dipole-dipole interaction in which hydrogen atoms serve as a bridge between two electronegative atoms, holding one by covalent bond and other by pure electrostatic forces.

$$X—H----Y$$

In this bond 'H' is covalently bonded to 'X' & ionically to 'Y'. The positive pole of one dipole is hydrogen atom ($X^{\delta-}—H^{\delta+}$).

The most frequent hydrogen bonds occur between —OH group and the —NH groups in the following order of decreasing stability.

$$OHH > OHO > NHN \equiv NHO$$

Hydrogen bonds may be intermolecular or intramolecular.

In aqueous medium, all free H-bonding groups on drug and receptors are linked to water through H-bonds.

The bond strength of H-bond is 1 to 7 kcal/mol.

Formation of H-bond leads to aqueous solubility of drug which is necessary for drug molecules to be transported to the site of action on a receptor

(3) Van der Waal's Forces
These are short range forces involving bonding interactions with non-polar groups. The bond strength may be 0.5 to 1.0 kcal/mol. In the medicinal agents, non-polar groups help in strengthening the drug-receptor interactions & in assuring the appropriate water-lipid solubility relationship.
London forces lead to bonding between two non-polar groups and are created from induced dipoles which arise from polarization of electron clouds.
when the non-polar moiety is of sufficient size and of appropriate steric configuration, London forces may stabilize a drug-receptor complex.

(4) Hydrophobic Bonding.
These are the most important interactions involved in maintaining the normal configuration of proteins and in determining the biological effect of many drugs. The bond strength of hydrophobic interactions is 1kcal/mol.
The interaction energy is related to gain in entropy for the system.
Each water molecule is H-bonded ~~to four other~~ with four bonds to neighbouring water molecules & is highly ordered.
~~For~~ For non-polar molecules the ~~~~

dipole-induced dipole bonding interactions is extremely weak and the energy gained is not enough to compensate for the increased ordering which results from dispersion of solute in water.

The non-polar solutes have low aqueous solubility and tend to aggregate in aqueous solution, freeing the ordered water molecules & thus increasing the entropy of the system. The complementary fit of a drug on receptor may require a close approach of non-polar residues, which can be facilitated only by freeing of water molecules between the two residues.

Hydrophobic bonding constant, $\pi = \log P_X - \log P_H$

where, P_X & P_H are partition coefficients of substituted and parent compounds respectively.

Positive π values increase hydrophobic bonding whereas negative π values decrease hydrophobic bonding.

Stereochemistry of D-R Interactions.

An exact fit of the drug molecule and receptor is necessary for maximum response. Most of the structurally specific drugs act stereospecifically when they exist as configurational isomers.

Theory of D-R Interactions

Receptor theory involves the enzyme kinetic

model based Law of mass action

$$k_d = \frac{[D][R]}{[DR]} \quad \text{Eq. 4-3}$$

The response of drug is ~~necessary~~ dependent on the number of receptors on a given tissue and the affinity of the receptor for drug.

Agonists bind to the receptor and lead to activation ~~action~~ of intracellular components involved in the physiological responsiveness of the cell or tissue.

Antagonists bind to the receptor and block the interaction of agonist. They donot produce effect of their own.

Inverse agonists interact with a defined recognition site on the receptor and are not only able to block the effects of agonist but are also able to produce their own effect opposite to the agonist.

Five theories have been proposed for D-R interaction (1) Occupancy theory (2) Rate theory (3) Inactivation theory (4) Induced-fit theory (5) Macromolecular perturbation theory.

Occupancy Theory

The basis of occupancy theory is that the effect produced by an agonist is dependent on the number of receptors occupied by the agonist. Using the Michalis-Menten derivation of law of mass action, the occupancy theory states that-

(i) the D-R complex is reversible ;
(ii) the association of drug with receptor to form D-R complex is a ~~biochem~~ bimolecular process while dissociation is unimolecular ;
(iii) all receptors of a class are equivalent and bind to the drug independent of each other ;
(iv) formation of D-R complex doesnot alter the affinity of the receptor for the drug ;
(v) the response is directly proportional to the number of receptors occupied ; and
(vi) the biological response is dependent on the attainment of equilibrium between the drug receptor.

The interaction of antagonist with the receptor results in occupancy without elicitation of a functional response.

Rate Theory.

According to the rate theory, the response due to an agonist drug depends on the rate of D-R complex formation. The effect 'E' is given as

$$E = \phi V_{eq} \qquad \text{Eq. 4-4}$$

The rate of D-R complex formation changes the receptor mediated events. The rate of association or dissociation of agonist is rapid and leads to sequence of impulses. Antagonist has high association rate ~~constant~~ bu

a low rate of dissociation.

Inactivation Theory

This theory is a hybrid of both occupancy and rate theory. This theory assumes that the D-R complex is an intermediate 'active' state that gives rise to an 'inactive' form of the receptor, R' that is part of an D-R complex [R'-D]
k_{+1} is rate of association of D-R
k_{-1} is rate of dissociation of D-R
k_2 is rate constant for transition of D-R to R'-D
nd the rate constant for regeneration of R from
R'-D is k_3

$$\begin{tikzcd}
{[D] + [R]} \arrow[r, shift left, "k_{+1}"] & {[D\text{-}R]} \arrow[l, shift left, "k_{-1}"] \arrow[dl, "k_2"] \\
{[R'\text{-}D]} \arrow[u, "k_3"] &
\end{tikzcd} \qquad \text{Eq}^n.\ 4\text{-}5$$

Now the response of drug is proportional to the rate of R' formation which is $k_3[R'-D]$.
t depends on both the rate of formation of
R' and the number of receptors occupied.

Induced Fit Theory

he occupancy & rate theories donot provide
pecific models at the molecular level to
ccount for drugs acting as agonist or antagonist.
e induced fit theory is based on induced-
t model of enzyme-substrate interaction leading
conformational change in enzyme and hence

active orientation of groups.
It assumes that protein constituents of the biologic membrane play a role in regulating ion flow.
The drug [for eg. Acetylcholine] may interact with the protein and alter the normal forces that stabilize the structure of the protein and hence produce a transient ~~change~~ rearrangem[ent] in the membrane structure and a consequen[t] change in its ion-regulating properties.

(V) <u>Macromolecular Perturbation Theory</u>
This theory is explained with the help of mode of action of acetylcholine at the muscarinic receptor.
Interaction of small molecules [drug] with a macromolecule [Receptor] may lead either to Specific Conformational Perturbations [SCP] or to non-specific Conformational Perturbations [NSCP].
A SCP results in the specific response of an agonist.
If an NSCP occurs, an antagonistic action m[ay] be produced.
If a drug possesses features that contribute to formation of both SCP and NSCP it results in partial stimulation action [partial agonist].

a low rate of dissociation.

Inactivation Theory

This theory is a hybrid of both occupancy and rate theory. This theory assumes that the D-R complex is an intermediate 'active' state that gives rise to an 'inactive' form of the receptor, R' that is part of an D-R complex [R'-D]

k_{+1} is rate of association of D-R

k_{-1} is rate of dissociation of D-R

k_2 is rate constant for transition of D-R to R'-D

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\begin{tikzcd}
{[D] + [R]} \arrow[rr, shift left, "k_{+1}"] & & {[D\text{-}R]} \arrow[ll, shift left, "k_{-1}"] \arrow[dll, "k_2"] \\
{[R'\text{-}D]} \arrow[u, "k_3"] & &
\end{tikzcd}
\qquad \text{Eq}^{n}.\ 4\text{-}5
$$

Now the response of drug is proportional to the rate of R' formation which is $k_3[R'-D]$. It depends on both the rate of formation of R' and the number of receptors occupied.

Induced fit Theory

The occupancy & rate theories donot provide specific models at the molecular level to account for drugs acting as agonist or antagonist. The induced fit theory is based on induced-fit model of enzyme-substrate interaction leading conformational change in enzyme and hence

active orientation of groups.

It assumes that protein constituents of the biologic membrane play a role in regulating ion flow.

The drug [for eg. Acetylcholine] may interact with the protein and alter the normal forces that stabilize the structure of the protein and hence produce a transient ~~change~~ rearrangement in the membrane structure and a consequent change in its ion-regulating properties.

V. Macromolecular Perturbation Theory

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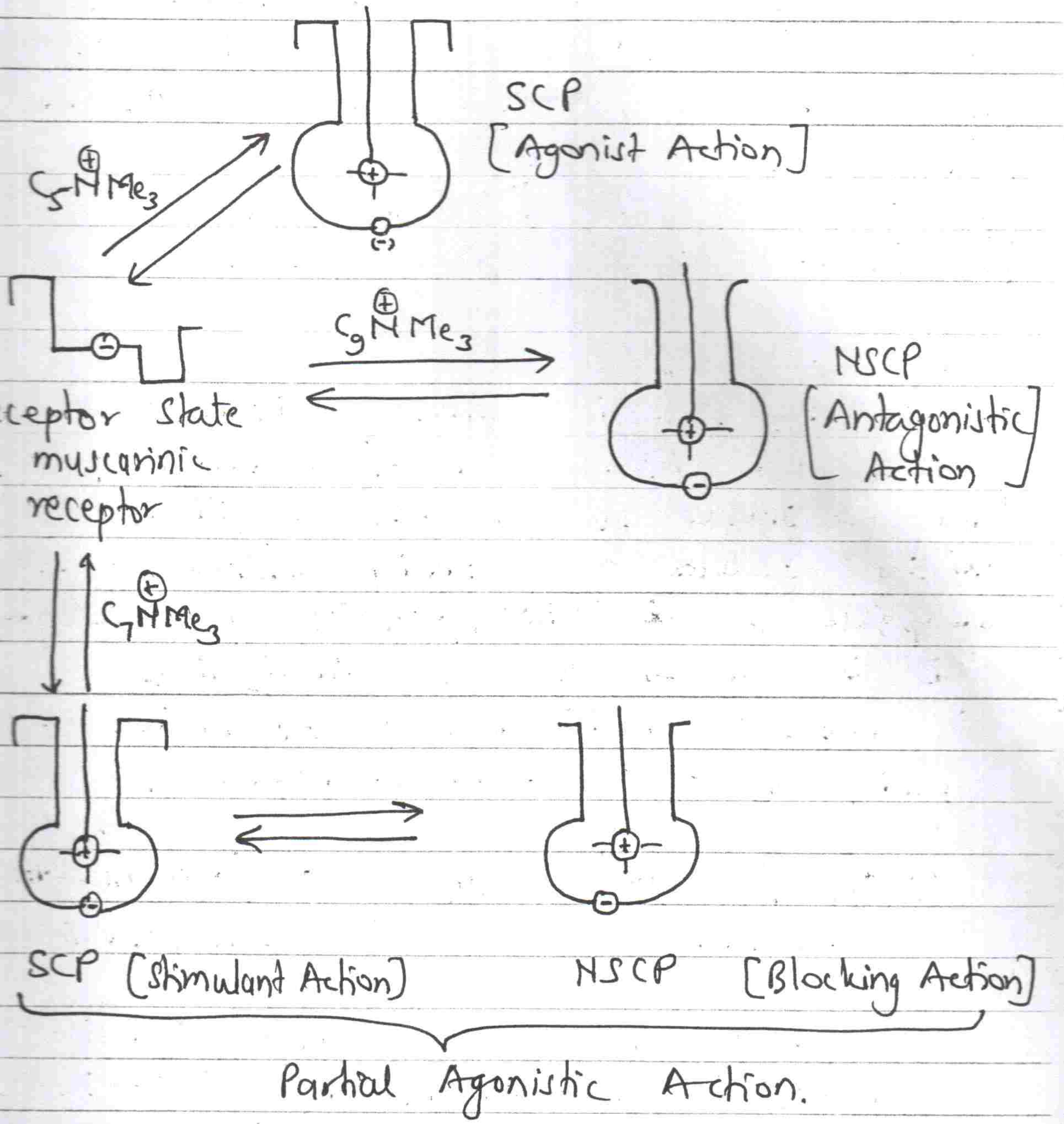
If a drug possesses features that contribute to formation of both SCP and NSCP it results in partial stimulation action [partial agonist].

Figure 4-1

Specific & Non specific Conformational Perturbations.



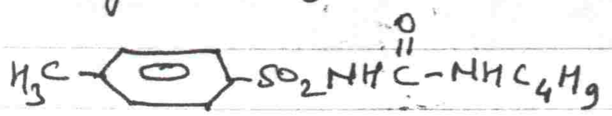
Chapter 5

Prodrugs

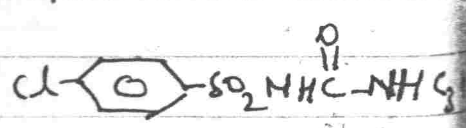
Almost all drugs possess some undesirable physicochemical properties and biological properties while designing a new drug delivery system three factors must be considered –
(i) drug component; (ii) vehicle / carrier; and (iii) intended route of administration.

Drug Component.

(1) Hard Drug : It is resistant to biotransformation and has a long biological half life. Design of a hard drug involves the metabolic stabilization of existing molecules by replacing functional groups susceptible to ~~bio~~ biotransformation by stable groups. This is also ~~is~~ called as derivatization.
For example : Stabilization of tolbutamide by replacing CH_3 by Cl as in chlorpropamide.



Tolbutamide



Chlorpropamide

(2) Soft Drug : It is a biologically active compound which is biotransformed invivo in a rapid and predictable manner into non-toxic metabolites.
Design of soft drugs involves the concept of metabolic ~~stab~~ switching in which a functional